ABSTRACTS

Gregory L. Moneta, MD, Abstracts Section Editor

Prospective evaluation of carotid bruit as a predictor of first stroke in type II diabetes: The Fremantle Study

Gillett M, Davis WA, Paxon D, et al. Stroke 2003;34:2145-51.

Conclusion: After detection of a carotid bruit in a patient with type II diabetes the risk for an initial stroke within 2 years is six times that in a patient with type II diabetes without a carotid bruit.

Summary: The Fremantle Diabetes Study is an observational, prospective, community based study of diabetes in western Australia. Between 1993 and 1996, 1081 patients with type II diabetes and no history of cerebrovascular disease were recruited and observed until the end of January 2002. Cox proportional hazards models were used to identify significant cerebrovascular risk factors for stroke and to determine whether carotid bruit was an independent predictor of first stroke in patients with type II diabetes.

After study entry, 134 patients (11.3%) developed a first stroke at a mean of 6.5 ± 2.2 years of follow-up. In the first 2 years after entering the study, a first stroke occurred in 45 patients (3.8%). After adjustment for cardiovascular risk factors and other potentially confounding variables, first stroke in the first 2 years after study entry was strongly predicted by the presence of carotid bruit (hazard ratio, 6.7; 95% confidence interval, 3.0-14.9; $P < .001$). After 2 years of study observation, first stroke was not associated with carotid bruit ($P = .97$). Both diastolic blood pressure and age were also determinants of first stroke in the first 2 years after study entry. Two years after study entry, age, atrial fibrillation or flutter, and microalbuminuria were independent predictors of stroke.

Comment: It might be concluded that patients with type II diabetes and carotid bruit compose a subgroup who will derive benefit from prophylactic carotid endarterectomy. However, the authors did not report the degree of carotid stenosis in their patients, and it is not clear that all strokes involved the extracranial cervical carotid artery. Clearly the data argue for aggressive risk factor management in patients with type II diabetes and a carotid bruit. The data, however, do not enable one to conclude that patients with a carotid bruit and type II diabetes will benefit from prophylactic carotid endarterectomy.

Carotid artery stenosis: Gray-scale and Doppler ultrasound diagnosis. Society of Radiologists in Ultrasound Consensus Conference

Grant EG, Benson CB, Moneta GL, et al. Radiology 2003;229:340-6.

Conclusion: A consensus conference convened by the Society of Radiologists in Ultrasound developed a set of criteria for grading internal carotid artery (ICA) stenosis with Doppler ultrasound scanning. Criteria are based primarily on ICA peak systolic velocity (PSV) and demonstration of presence of plaque on gray-scale and color Doppler scans.

Summary: A multidisciplinary panel was charged to develop a set of reasonable criteria for Doppler diagnosis of ICA stenosis. Criteria proposed were based on review of the literature and presentations at the conference. Recommendations included:

1. Use of gray-scale, color Doppler scanning and spectral Doppler ultrasound scanning for all carotid artery examinations
2. Stratification of ICA stenoses into six categories:
   a. Normal: ICA PSV less than 125 cm/s, with no visible plaque or intimal thickening
   b. Less than 50% stenosis: ICA PSV less than 125 cm/s, with visible plaque or intimal thickening
   c. 50% to 69% stenosis: ICA PSV 125 to 230 cm/s, with visible plaque
   d. ICA stenosis greater than 70% to near occlusion: ICA PSV greater than 230 cm/s, with visible plaque and luminal narrowing on gray-scale and color images
   e. Near occlusion: color Doppler scan showing an extremely narrow lumen
   f. Total occlusion: no detectable lumen on gray-scale ultrasound scans and no flow on color, power, or spectral Doppler scans

ICA–common carotid artery PSV ratio and ICA end-diastolic velocity may also be used when it appears that ICA PSV may not represent the extent of stenosis.

Comment: The conference consisted of panelists from radiology, neurology, vascular surgery, vascular medicine, and interventional radiology, among other specialties. Results represent what the panelists considered to be reasonable criteria for ICA stenosis. It is suggested that these criteria be considered by laboratories with insufficient angiographic material for validation of existing published criteria. The proposed criteria have not been tested, and do not represent the results of any single publication. Laboratories using published criteria validated locally are urged to continue to use them.

Subcutaneous Fondaparinux vs intravenous unfractionated heparin in initial treatment of pulmonary embolism

Matisse Investigators. N Engl J Med 2003;349:1695-1702.

Conclusion: Fondaparinux, given as once daily subcutaneous treatment without monitoring, was as effective and as safe as intravenously administered unfractionated heparin for treatment of hemodynamically stable patients with symptomatic pulmonary embolism.

Summary: Fondaparinux is an antithrombotic synthetic agent with specific anti–factor Xa; activity. It is administered as a single daily subcutaneous injection, and does not require monitoring of the anticoagulation effect. This was an open-label trial of 2213 hemodynamically stable patients with acute symptomatic pulmonary embolism. Pulmonary embolism was diagnosed on the basis of findings of computed tomography, pulmonary angiography, high-probability ventilation perfusion scanning, or a nondiagnostic lung scan with either duplex ultrasound scanning or venographic diagnosis of deep venous thrombosis. Patients received either unfractionated intravenous heparin via continuous infusion, with a target partial thromboplastin time of one and a half to two and a half times control, or daily subcutaneous Fondaparinux at a fixed weight-adjusted dose. Both drugs were given for 5 days until oral anticoagulation therapy resulted in an international normalized ratio greater than 2.0. The primary end point was symptomatic recurrent pulmonary embolism or new or recurrent deep venous thrombosis at 3 months.

New or recurrent pulmonary embolism or deep venous thrombosis occurred in 42 of 1103 patients receiving Fondaparinux (3.8%) and in 56 of 1110 patients receiving unfractionated heparin (5.0%). Major bleeding occurred in 1.1% of those given heparin and in 1.3% of those given Fondaparinux. Mortality at 3 months was 5.2% in the Fondaparinux group, and 4.4% in the heparin group. In the Fondaparinux group 14 patients died of pulmonary embolism within 3 months, compared with 15 patients in the heparin group.

Comment: The study demonstrates therapeutic equivalence of Fondaparinux and continuous infusion of intravenous unfractionated heparin in the initial management of symptomatic pulmonary embolism in hemodynamically stable patients. A single daily subcutaneous dose, combined with no need for monitoring of the anticoagulant effect, makes Fondaparinux an attractive alternative for initial management of uncomplicated pulmonary embolism.

Effective treatment of carotid artery stenosis on blood pressure: A comparison of hemodynamic disturbances after carotid endarterectomy in endovascular treatment

McKebitt FN, Sivaguru A, Venables GS, et al. Stroke 2003;34:2573-82.

Conclusion: Carotid endarterectomy and endovascular treatment of carotid artery stenosis both affect blood pressure stability during the first 24 hours after the procedure. Compared with preoperative baseline levels, systolic blood pressure at 6 months is lower in patients who undergo surgery, and is unchanged in patients who undergo endovascular treatment.

Summary: Periprocedure and long-term blood pressure effects of carotid endarterectomy and endovascular treatment of carotid artery stenosis were studied in patients randomized at a single center in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). Patients were randomized to endovascular treatment of carotid stenosis (n = 55) or carotid endarterectomy (n = 49). Ambulatory 24-hour blood pressure monitoring was recorded before carotid intervention and at 24 hours, 1 month and 6 months after intervention. Hypotension and hypertension were defined as a decrease or increase, respectively, in systolic blood pressure of 30 mm Hg or greater from baseline blood pressure recordings.

After the procedure, in the first 24 hours hypotension occurred in 76% of the endovascular group and 75% of the carotid endarterectomy group, and hypertension occurred in 13% and 11%, respectively. At 1 hour systolic blood pressure decreased by a mean of 24 mm Hg in the surgical group and 16 mm Hg in the endovascular group; however, the decrease was sustained only in the endovascular group ($P < .0001$). At 6 months systolic pressure was at baseline in the endovascular group, and was 5 mm Hg lower in the surgical group. Thirty-day stroke and mortality rate was 10.2% in the surgical group, and 5.5% in the endovascular group. Perioperative neurologic complication was not related to perioperative hemodynamic disturbance.

Comment: The study suggests a difference in blood pressure response after surgical versus endovascular therapy for carotid artery stenosis. In surgical patients, however, a specific protocol was used to reverse hypotension, whereas no specific protocol was used in the stent group. The 6-month data are difficult to interpret, because there is no follow-up information on

number and dosage of antihypertensive medications in either group. This study should be regarded as hypothesis-seeking, and does not definitively establish a difference in blood pressure response after carotid endarterectomy versus carotid stenting.

Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease

Mohler ER, Hiatt WR, Creager MA, and Study Investigators. Circulation 2003;108:1481-6.

Conclusion: Atorvastatin improves pain-free walking distance as measured with treadmill testing in patients with intermittent claudication.

Summary: This was a randomized, double-blind, parallel-design study of 354 patients with intermittent claudication secondary to peripheral arterial disease. Patients were given either placebo, or 10 or 80 mg/d of atorvastatin for 12 months, and evaluated in terms of treadmill exercise time, ankle brachial index, self-reported measures of physical activity, and quality-of-life questionnaires.

Atorvastatin did not change maximal treadmill walking time after 12 months of treatment. Pain-free walking time was improved with the 80-mg dose of atorvastatin ($P = .025$) compared with placebo. There were no differences in ankle-brachial index between the three groups at 12 months. Twelve vascular events occurred during follow-up: 9 in the placebo group, 1 in the 10-mg atorvastatin group, and 2 in the 80-mg atorvastatin group. Vascular events were higher in the placebo group than in the combined Atorvastatin groups ($P = 0.003$). Both the 80-mg and 10-mg atorvastatin groups demonstrated improved physical activity compared with the placebo group. There were no differences in quality of life as measured by the short-form health survey (36 items) and Walking Impairment Questionnaire.

Comment: The heart protection study (Lancet 2002;360:7-22) demonstrated a reduction in risk for death and adverse cardiac events in patients with peripheral arterial disease without a previous cardiovascular event who were treated with simvastatin. The current study also indicates that a statin, atorvastatin, can improve pain-free walking distance and physical activity in patients with intermittent claudication. Regardless of cholesterol level, it is highly likely that all patients with symptomatic or asymptomatic atherosclerosis will benefit from a statin medication.

Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: A phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication

Rajagopalan S, Mohler ER, Lederman RJ, et al. Circulation 2003;108: 1933-8.

Conclusion: A single set of intramuscular injections of adenoviral vascular endothelial growth factor 121 (adVEGF121) did not result in exercise improvement, increased ankle-brachial index, or improved quality of life in patients with intermittent claudication.

Summary: Growth of new blood vessels to improve symptomatic ischemia is termed therapeutic angiogenesis. This trial, the Regional Angiogenesis with Vascular Endothelial Growth Factor (RAVE) trial was the first major randomized study to evaluate the safety and efficacy of adVEGF121 gene transfer in treatment of peripheral vascular disease.

A replication-deficient adenovirus encoding the 121 amino acid isoform of VEGF was injected into the lower extremities of subjects with unilateral peripheral arterial disease. The 105 patients were stratified on the basis of diabetic status. All had unilateral exercise-limiting intermittent claudication, and were randomized to either high-dose or low-dose adVEGF121 therapy or placebo. Drug was given as 20 intramuscular injections in the ipsilateral leg in a single session.

At 12 weeks there were no differences in change in peak walking time among the placebo, low-dose, and high-dose groups. In addition, secondary end points of ankle-brachial index, claudication onset time, and quality-of-life assessment (short-form health survey [36 items] and Walking Impairment Questionnaire) did not differ among the groups at 12 and 26 weeks. No major safety issues were identified through 1 year of follow-up.

Comment: Several possible impairments to adenoviral transfection of adult skeletal muscle may have contributed to the negative results of this study. Possible impairments to transfection include muscle fascia, connective tissue, and lower concentrations in skeletal muscle of the Coxsackie adenoviral receptor. Angiogenesis for treatment of peripheral arterial disease is still more an interesting idea than practical reality.

Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor Ximelagatran

Schulman S, Wahlander K, Lundstrom T, et al. N Engl J Med 2003;349: 1712-21.

Conclusion: Ximelagatran, an oral direct thrombin inhibitor, is superior to placebo in preventing recurrent venous thromboembolism, with no increase in bleeding complications.

Summary: In a multicenter, double-blind trial, 1233 patients with venous thromboembolism who had undergone 6 months of standard oral anticoagulant therapy were randomly assigned to an additional 18 months of treatment with either placebo or 24 mg twice daily of Ximelagatran. The primary end point was recurrent venous thromboembolism. The two groups were compared with respect to recurrent venous thromboembolism events and hemorrhagic complications.

Of the 612 patients assigned to the Ximelagatran group, a primary end point was reached in 12 patients. In the 611 patients assigned to the placebo group, a primary end point was reached in 71 patients (hazard ratio, 0.16; 95% confidence interval, 0.09-0.30; $P < .001$).

There were six deaths in the Ximelagatran group, and seven deaths in the placebo group. Bleeding occurred in 134 patients given Ximelagatran, and in 111 control patients (hazard ratio, 1.19; 95% confidence interval, 0.93-1.53; $P = .17$). Major hemorrhage was infrequent, occurring in 6 patients in the Ximelagatran group and 5 patients in the placebo group.

There were three fatal pulmonary emboli in the placebo group, compared with none in the Ximelagatran group. There was a cumulative risk for transient elevation of alanine aminotransferase concentration to more than three times normal in 6.4% of the Ximelagatran group and 1.2% of the placebo group ($P < .001$). Increase in aminotransferase levels was transient, restricted to the first 4 months of therapy, and did not result in progressive hepatic dysfunction. Levels decreased spontaneously whether or not Ximelagatran was continued.

Comment: Ximelagatran, unlike warfarin sodium, does not have any clinically important known food or drug interactions. This drug, with an overall safety profile comparable to that with placebo and no need for laboratory monitoring, appears to be a low-risk, effective method for preventing recurrent venous thromboembolism. Rat poison may once again be relegated to rats.

Risk factors for death or stroke after carotid endarterectomy: Observations from the Ontario Carotid Endarterectomy Registry

Tu JV, Wang H, Bowyer B, et al, and participants in the Ontario Carotid Endarterectomy Registry Stroke 2003;34:2568-75.

Conclusion: A history of transient ischemic attack or stroke, contralateral occlusion, diabetes, atrial fibrillation, and congestive heart failure are independent predictors for increased risk for stroke or death at 30 days after carotid endarterectomy.

Summary: The study used data derived from the Ontario Carotid Endarterectomy Registry, which contains information on all carotid endarterectomy procedures performed in Ontario, Canada, in calendar years 1994 to 1997. Medical records of all 6038 patients undergoing carotid endarterectomy during this period were abstracted for patient characteristics and 30-day perioperative stroke and death. Data from 34 hospitals and 102 surgeons are represented in the study.

Overall 30-day stroke and death rate was 6.0%. Independent predictors of 30-day stroke or death included history of transient ischemic attack or stroke (odds ratio [OR], 1.75; 95% confidence interval [CI], 1.39-2.20), contralateral carotid occlusion (OR, 1.72; 95% CI, 1.25-2.38), atrial fibrillation (OR, 1.89; 95% CI, 1.29-2.76), congestive heart failure (OR, 1.80; 95% CI, 1.15-2.81), and diabetes (OR, 1.28; 95% CI, 1.01-1.63). Assigning 1 point to each independent predictor, a total of 4 points was associated with a 15.8% perioperative risk for stroke or death, whereas the absence of all of the above independent predictors predicted a 3.3% perioperative risk for stroke or death.

Comment: This report can help determine which of the growing number of patients said to be at "high risk" are truly at high risk for perioperative complication after carotid endarterectomy. Like all observational studies, this study is subject to selection bias, inasmuch as no information is provided regarding patients who were considered for carotid endarterectomy but did not undergo the procedure.

Future studies must concentrate, not only on identifying patients who are at high risk for carotid intervention, but also on identifying patients who are at particularly high risk for withholding intervention.